

REMARKS

The claims are 19-26, with claim 19 being the sole independent claim. Method claims 25 and 26 are withdrawn from consideration pending allowance of the elected composition claims. Claims 1-18 have been cancelled without prejudice or disclaimer. Support for claims 19-26 may be found in claims 1-18 and in the specification at page 13, lines 16-21 and at page 14, lines 16-18.

Although cancellation of claims 1-18 renders the rejections in the outstanding rejection moot, Applicants will address the rejections to the extent that they apply to the pending claims.

Previously pending claims 10-14 and 16 were rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicants note that the terms “compound” and “other antidiabetic agent” are not present in the newly presented claims.

Previously pending claims 10-14 and 16 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martini et al. WO 03/068195 and Lewis et al. US 2004/0081697. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the currently claimed oral dosage form is non-obvious when considering the state of the art and in particular the combination of WO‘195 and US‘697.

WO‘195 publication discloses a sustained release oral dosage form that comprises an erodable core comprising rosiglitazone surrounded by an enteric coating with openings leading to the core. This particular formulation is designed to enable “the delivery of drug substances which exhibit pH dependent solubility, in particular compounds that are more soluble at low pH levels( less than pH2) than at near neutral levels (greater than about pH5)” (page 1, lines 12 to 14).

US‘697 publication discloses modified release compositions (including delayed, sustained and pulsed release) comprising rosiglitazone and other antidiabetic agents (one of which may be metformin). There is no disclosure or suggestion of how to overcome any formulation issues involving these two active ingredients.

In particular, neither WO‘195 nor US‘697 discloses or suggests how to effectively solve the problem of creating a single oral dosage form that provides for controlled release for two active ingredients, where each of the ingredients have substantially different solubility profiles. Rosiglitazone is far more soluble in the acidic conditions of the

stomach (around pH 2) than in the near neutral conditions of the upper intestine (greater than pH5). Metformin, on the other hand, is soluble over a wide range of physiological pH, but has a narrow window of absorption in the upper intestine rather than the stomach or lower intestine. A further complication is the different dosage ranges of the two actives: rosiglitazone is administered in 2-8mg doses whereas metformin is administered in 500-1000mg doses.

Therefore, the problem remaining to be solved over the cited prior art is the provision of an oral dosage form which compensates for the pH dependent solubility of rosiglitazone and the narrow absorption window of metformin, while maintaining consistent and accurate dose delivery of both active ingredients, such that the patient need only take one daily dose.

The combination of WO‘195 and US‘697 gives the person skilled in the art a number of modified release formulations to choose from, sustained, delayed or pulse release and a number of antidiabetic agents that could be paired with rosiglitazone (of which metformin is only one).

The currently claimed invention is a sustained release formulation that comprises rosiglitazone and metformin such that the active ingredients can be dosed once daily, improving patient compliance.

The use of a coating with an opening in it means that while the dosage form is in the stomach (on average from 4-5 hours) there is a steady release of both active ingredients from the core into the stomach. During this time the stomach contents slowly drain into the upper intestine. This means that soluble rosiglitazone and metformin released from the dosage form trickles through into the upper intestine where they are readily absorbed. Once the stomach empties and what's left of the dosage form passes through to the upper intestine the enteric coat dissolves and releases what remains of the core. Metformin is highly soluble and highly absorbed in the upper intestine. Although rosiglitazone has a low solubility in this environment some of the rosiglitazone has already been absorbed by the body, leaving less of the compound needing to be dissolved in this environment. Moreover, as more and more of the soluble rosiglitazone is absorbed, more and more of the rosiglitazone is able to dissolve and therefore become available for absorption as the compound moves through the upper intestine. The claimed dosage form therefore enables the correct doses of both actives to be delivered to the body in such a manner as to compensate for the differences between them.

In summary, the inventors have created an oral dosage form that can be administered once a day and allows modified release of both rosiglitazone (narrow solubility window, low dose) and metformin (narrow absorption window, huge dose).

Re: Examiner's Response to Arguments

Applicants wish to clarify their argument that WO'195 and US'697 fail to describe or otherwise provide sufficient motivation for one skilled in the art to consider these references in combination.

In particular, when Applicants argued that the claimed oral dosage form comprises more than just an erodable core containing rosiglitazone and metformin, Applicants were not suggesting that the dosage form contained another active ingredient, rather, that the oral dosage form possessed other components, such as those defined in paragraph (ii) of claim 19.

Moreover, Applicants respectfully submit that there is insufficient basis for the contention that it would have been obvious to the skilled artisan to try to include metformin in the dosage form taught by WO'195 - specifically, because WO'195 teaches away from such a combination.

The Examiner states that it is well known in the art that rosiglitazone does not alter the pharmacokinetics of metformin and that co-administration of these drugs is known in the art. However, the art discloses administering these drugs in separate formulations or discloses co-administration in other formulations (e.g., potentially those described in US'697).

WO'195 discloses a sustained release oral dosage form that was designed for delivery of a pharmaceutically active weak base – defined at page 3, lines 4-15 as a base “the conjugate acid of which has a pKa of less than 11.5.” Metformin possesses a pKa of 12.4. No reason has been provided for why one skilled in the art would look at the formulation described in WO'195 as being suitable or desirable for delivery of a drug substance, the conjugate acid of which has a pKa of greater than 11.5.

Reconsideration of the Section 103 rejection is respectfully requested.

In view of the above amendments and remarks, reconsideration of this application is requested. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number below.

Respectfully submitted,

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